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AMENDMENT

IN THE CLAIMS:

Please cancel claims 1-3, 5-10 and 17-25 without prejudice or disclaimer.

Please amend claims 4, 11-16 and 26-28 as follows:

4. (Amended) A process for generating a combinatorial library, comprising the steps of:

- A3
- (a) preparing a plurality of immobilized molecules selected from a nucleoside and a nucleotide; wherein each molecule contains 3 to 10 reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups on each immobilized molecule are independently removable under at least three different conditions; and
 - (b) removing each blocking group and derivatizing the resulting reactive moiety in a preprogrammed, regioselective manner; wherein each member of the plurality of immobilized molecules is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial library.

11. (Amended) A process of claim 4, wherein the reactive moieties are selected from OH, SH, NH₂, CO₂H, SOH, SO₂H, SO₃H, CHO, keto, phosphate, phosphite, phosphoramidite, halogen, CN, CNS, NCS and NCO.

12. (Amended) A process of claim 4, wherein the immobilized molecules have been immobilized based on linkage to a solid support.

A4

13. (Amended) A process of claim 12, wherein the solid support is selected from beads, flat supports, wafers with pits, wafers without pits, wafers with channels, wafers without channels, bottom surface of a microtiter plate, and inner walls of a capillary.

14. (Amended) A process of claim 13, wherein the beads are comprised of a material selected from polystyrene, polyamide, cellulose, agarose, dextran cross-linked with epichlorohydrin, silica gel, controlled pore glass (CPG), and polytetrafluoroethylene.

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Claims 4, 11-16 and 26-28 are amended herein. Basis for the amendments to the claims may be found, for example, in the claims as originally filed. Claims 4 and 26 have been rewritten as independent claims incorporating the limitations of the base claims.

TRAVERSAL OF LACK OF UNITY OBJECTION

Applicant respectfully traverses the Lack of Unity Objection as between Groups I and IV. Applicant has filed a Petition under 37 C.F.R. §1.144 requesting removal of the Lack of Unity Objection as between Groups I and IV, and also requesting removal of the finality of the Objection as being premature. The Petition was filed April 26, 2001, *i.e.*, within 2 months of the mailing date of the instant Office Action.

This application is the U.S. national stage of International Patent Application No. PCT/US97/06509, in accordance with 35 U.S.C. §371. As stated in MPEP 201, national stage applications of international applications are similar to national applications, but there are differences. Among these differences is inapplicability of restriction practice to national stage applications. Restriction practice is applied to national applications, but unity of invention practice is applied to national stage applications (see, MPEP 201 and MPEP 1893.03(d)).

LACK OF UNITY OF INVENTION

Applicant respectfully traverses the Lack of Unity Objection as between Groups I and IV in view of the following remarks. In addition, it is respectfully submitted that the finality of this holding is premature.

Group I, claims 1, 3, 4 and 11-16, is directed to a process of generating a combinatorial set of core molecules of core structure M and a combinatorial set of compounds with core structure M. Group IV, claims 23-36, is directed to a combinatorial set of compounds with core structure M.

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PCT Rule 13

This application is the U.S. national stage of International Patent Application No. PCT/US97/06509, in accordance with 35 U.S.C. §371. Applicant notes that no lack of unity objection was raised during either Chapter I or II at the international stage.

As stated in MPEP 201, national stage applications of international applications are similar to national applications, but there are differences. Among these differences is inapplicability of restriction practice to national stage applications. Restriction practice is applied to national applications, but unity of invention practice is applied to national stage applications (see, MPEP 201 and MPEP 1893.03(d)). Therefore, the applicable rule with respect to the instant national stage application is PCT Rule 13.1.

Lack of Unity Standard

When the U.S. Patent Office considers an international application during the national stage, restriction must be based on unity of invention, which is governed by PCT Rule 13 (see MPEP 1893.03(d); Caterpillar Tractor Co. v. Commissioner of Patents and Trademark, 650 F. Supp. 218, 31 USPQ 590 (E.D. Virginia, 1986); In re Caterpillar Tractor Co., 228 USPQ 77). In the Caterpillar cases it was ultimately held that the language in Rule 13.1 "specially adapted" is not to be interpreted as meaning that the process of manufacture can only be used to manufacture the product because this interpretation is in conflict with the PCT Rule, which provides that no national law shall require compliance with requirements relating to the form or contents of the international application different from or additional to those which are provided in the Treaty (Article 27 of the PCT). Thus, the U.S. Patent Office cannot impose requirements that differ from those provided in the Treaty. Since restriction practice differs from and is more restrictive than unity of invention, the unity of invention rules must govern.

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Therefore, it is respectfully submitted, and it appears that the Office has acknowledged, that the rules of unity of invention (PCT Rule 13.1 and 37 C.F.R. §1.475) apply to this application. Rule 13.1 requires that an international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

Groups I and IV do not lack unity under PCT Rule 13

It is respectfully submitted that Groups I and IV relate to a product and a process for the manufacture of said product, and therefore do not lack unity of invention under PCT Rule 13.

Groups I and IV are directed to a process for generating a combinatorial set of molecules of core structure M, and a combinatorial set of compounds with core structure M, respectively. Such groups of claims do not lack unity of invention under PCT Rules 13.1 and 13.2. See 37 CFR §1.475(b):

An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

- (1) A product and a process specially adapted for the manufacture of said product...

The claims of Group IV are directed to a product (a combinatorial set of compounds with core structure M), and the claims of Group I are directed to a process for the manufacture of the product (a process for generating a combinatorial set of molecules of core structure M). Such Groups of claims do not lack unity of invention, and therefore should be examined in one application.

Applicant respectfully requests reconsideration of the lack of unity objection as between Groups I and IV. In view of Applicant's election of Group I, it is respectfully requested that the claims of Groups I and IV, i.e., claims 1, 3, 4, 11-16 and 23-36, be examined in the instant application.

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See also, the sixth paragraph of MPEP 1893.93(d):

A process is "specially adapted" for the manufacture of a product if the claimed process inherently produces the claimed product with the technical relationship being present between the claimed process and the claimed product. The expression "specially adapted" does not imply that the product could not also be manufactured by a different process.

Lack of Novelty of Group I

While appearing to agree with the above, the Office Action alleges that the claims of Groups I and IV lack unity of invention because the claims of Group I allegedly are not novel. Applicant respectfully disagrees.

The Office Action, mailed February 26, 2001, urges that the Objection is based on the allegation that synthesis of combinatorial libraries of compounds using solid supports and blocking groups is well known in the art. As stated in the Office Action:

The traversal is on the ground(s) that the special technical feature of group I is not taught by the prior art. This is not found persuasive. Applicants point out that Carell et al. do not teach combinatorial synthesis based on immobilized molecules. Applicants arguments have been considered. However, it is well known in the art to synthesize combinatorial library of compounds using solid supports and blocking groups. Thus, the inventions lack unity.

The Office Action does not dispute Applicant's argument that Carell et al., cited previously by the Office, does not anticipate Group I, and therefore does not destroy the unity of invention as between Groups I and IV. The Office Action alleges that the subject matter of the claims of Group I is well known in the art and therefore lacks novelty. Applicant respectfully disagrees. The Office Action fails to cite any art relating to the novelty of the claims of Group I. The Office Action improperly relies on a bare allegation to allege lack of novelty of the claims of Group I.

The Office Action improperly relies on a bare allegation

The Office Action provides no support for the bare allegation that "it is well known in the art to synthesize combinatorial library of compounds using solid supports and blocking groups." As stated in MPEP 2144.03, citing in re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418,420-421 (CCPA 1970), "[A]ssertions of technical facts in areas of esoteric technology must always be supported by citation of some reference work" and "allegations concerning specific 'knowledge' of the prior art, which might be peculiar to a particular art should also be supported." No support for the allegation that "it is well known in the art to synthesize combinatorial library of compounds using solid supports and blocking groups" is provided. Applicant respectfully requests that the Examiner provide support for the allegation. If no support is provided, then the it is respectfully requested that the allegation, and the Objection, be withdrawn.

The claims of Group I are novel over the bare allegation of the Office Action

Moreover, even if the bare allegation of the Office Action is correct, which Applicant does not admit, such allegation does not anticipate the claims of instant Group I and thus does not destroy unity of invention as between Groups I and IV. The claims of Group I are directed to a process for generating a combinatorial set of molecules of core structure M by:

- (a) preparing a plurality of immobilized molecules of core structure M, wherein said molecules contain a plurality of reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups are independently removable under at least three different conditions, and
- (b) removing certain blocking groups and derivatizing the resulting reactive moieties in a preprogrammed, regioselective manner, wherein each member of a combinatorial set is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial set of molecules of core structure M.

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It is respectfully submitted that the bare allegation of the Office Action does not anticipate this claim. Instant claim 1 requires use of three blocking groups that are independently removable under at least three different conditions in a preprogrammed, regioselective manner. Furthermore, instant claim 1 requires that each member of the combinatorial set produced by the claimed process be uniquely derivatized at at least one reactive moiety with a unique substituent. The bare allegation of the Office Action that "it is well known in the art to synthesize combinatorial library of compounds using solid supports and blocking groups" does not recite these limitations. Therefore, the bare allegation of the Office Action, if accepted as true, does not anticipate the claims of instant Group I, and also does not destroy the unity of invention as between Groups I and IV.

Applicant respectfully petitions for removal of the lack of unity objection as between Groups I and IV, and that these Groups be combined for examination in the instant application.

The finality of the Objection is premature

Furthermore, irrespective of whether the arguments presented in the Office Action are correct or not, the finality of the Objection is premature. The Office Action alleges for the first time that "it is well known in the art to synthesize combinatorial library of compounds using solid supports and blocking groups." Thus, the Office Action has provided a new basis for the allegation of lack of unity of invention while simultaneously making the Objection final. Applicant has not been provided an opportunity to respond to the new basis for the Objection. Therefore, it is respectfully submitted that the finality of the Objection is premature.

Summary

Applicant respectfully requests reconsideration and removal of the lack of unity objection as between Groups I and IV. It is respectfully submitted that the Objection as between Groups I and IV is improper because the Groups are

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related as a product and a process specially adapted for preparation of the product. Such related Groups do not lack unity of invention within the meaning of PCT Rule 13.1.

Furthermore, the bare assertion of the Office Action does not anticipate the claims of instant Group I, and, therefore, does not destroy the unity of invention as between Groups I and IV. Also, the finality of the Objection is premature because Applicant has not had the opportunity to respond to the new basis for the Objection set forth in the Office Action.

As noted above, applicant has also submitted a Petition pursuant to 37 C.F.R. §1.144 that was timely filed within 2 months from the mailing of the Office Action requesting reconsideration and removal of the finality of the Lack of Unity Objection.

REQUIREMENT FOR ELECTION OF SPECIES

Applicant respectfully requests removal of the Requirement for Election of Species. It is respectfully submitted that, as described in detail below, the species are so linked as to form a single general inventive concept within the meaning of PCT Rule 13.1 (see, MPEP 1893.03(d)). It is noted that nothing herein should be construed as an admission that the various species present in the instant claims are obvious variants of each other. Furthermore, it is respectfully submitted that the requirement for election of a single species is inconsistent with the subject matter of the instant claims.

Unity of Invention

This application is the U.S. national stage of International Patent Application No. PCT/US97/06509. Therefore, PCT regulations with respect to unity of invention are applicable herein (see, PCT Rule 13, 37 CFR §1.475, and MPEP 1893.03(d)). Unity of invention is based on the basic principle that an applicant has the right to include in a single application those inventions (e.g., species) which are so linked as to form a single general inventive concept (MPEP 1893.03(d)). Applicant respectfully submits that, given the subject

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matter of the instant claims, the building blocks (e.g., nucleosides), reactive groups, and protecting groups are so linked as to form a single general inventive concept. Therefore, a requirement to elect a single species in each of these elements is inappropriate.

The instant claims are directed to a combinatorial protecting group strategy for multifunctional molecules. In particular, the claims are directed to products and processes for oligonucleotide synthesis and for preparation of combinatorial libraries. Restriction of the claims to the single species required in the Office Action would negate a fundamental aspect of the subject matter of the instant claims (i.e., the combinatorial aspect).

Restriction of Monomers

The instant claims are directed to products and processes for preparation of the products, where the products are a combinatorial set of molecules of core structure M, or a composition comprising an oligomer. In particular, the claims are directed to (1) oligomers comprising not only of one moiety, but in the case of oligonucleotides, of at least all four of the natural building blocks, and (2) within the oligomer, using different protecting groups at different positions within the oligomer chain (even at the same type of building block).

As described in detail in the application, such products are useful as drugs. Modified oligonucleotides are used in an antisense/triplex DNA approach. Modifications are necessary to provide oligonucleotides of desired cell and nuclear transport properties, while retaining the desired activity. The instant processes provide such various products in a preprogrammed, specific manner requiring only one oligonucleotide synthesis run. In order to fully utilize the products and processes of the instant claims, use of various monomers is required.

Therefore, restriction of the claims to only a single building block, particularly where the products are oligonucleotides, (e.g., a single disclosed species from claim 10; a single disclosed species representing B or B^{R2A} or B^{R2B};

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or a single disclosed species from claim 31) is not appropriate since these building blocks are all part of a single general inventive concept. The claims are directed to compositions and combinatorial libraries containing oligonucleotides, and processes for preparation of same. If Applicant were required to elect a single disclosed nucleoside species as required, then the search, and any resulting allowed claims, would be limited to oligonucleotides containing only the single elected nucleoside (i.e., TTTTTTT..., GGGGGG..., AAAAAA..., CCCCCC..., etc.). Such a requirement is inconsistent with the subject matter of the instant claims, and violates Applicant's right to have all species that form a single general inventive concept included in a single application.

Restriction of Reactive Groups and Protecting Groups

Furthermore, the application is directed to a combinatorial protecting group strategy for multifunctional molecules. Restriction to a single reactive group or a single protecting group is inconsistent with the subject matter of the instant claims.

Restriction of the claims to only a single reactive group, e.g., a reactive group of claims 11 or 24, is not appropriate because the claims are directed to products and processes that have different protecting groups at different positions (i.e., on different reactive groups) within the product. To restrict the reactive groups to a single reactive group would negate a fundamental aspect of the instant claims. The different reactive groups are part of the single general inventive concept of the instant claims.

Restriction of the claims to only a single protecting group, e.g., a single R^{4A} or R^{4B} group; or a single R^{2A} or R^{2B} group; or a single group for R³; is also not appropriate because the claims are directed to different protecting groups at different positions within the product. To restrict the reactive groups to a single reactive group would negate a fundamental aspect of the instant claims. The different protecting groups are part of the single general inventive concept of the instant claims.

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Therefore, requiring election of a single disclosed reactive group or protecting group is inconsistent with the subject matter of the instant claims. Moreover, such requirement violates Applicant's right to have all species that form a single general inventive concept included in a single application (see, MPEP 1893.03(d)).

Summary

For the reasons given above, Applicant respectfully requests removal of the lack of unity objection as between Groups I and IV. Furthermore, Applicant respectfully requests removal of the lack of unity objection as relating to the requirement for election of a single species.

Applicant has also submitted a Petition pursuant to 37 C.F.R. §1.144 that was timely filed within 2 months from the mailing of the Office Action requesting reconsideration and removal of the finality of the Lack of Unity Objection and the Requirement for Election of Species.

DRAWINGS

The Office Action notes that the application was filed with informal drawings. Formal drawings will be submitted at the appropriate time. Any necessary amendment to the specification will be made at that time.

OBJECTION TO THE SPECIFICATION

The Office Action objects to the specification for allegedly failing to provide antecedent basis for the types of solid supports claimed in claim 14. Applicant has amended the specification herein to provide basis for the supports of claim 14. Therefore, it is respectfully submitted that this objection has been overcome.

TRADEMARKS

The Office Action notes that certain trademarks appear in the application and requires that such be properly capitalized and accompanied by generic terminology. Applicant has herein amended the specification to properly identify the registered trademarks WATERS NOVA-PAK C18[®], MILLENIUM[®],

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TEFLON[®], SEPHAROSE[®] and SEPHADEX[®], and to provide generic terminology for these marks.

REJECTION OF CLAIMS 1, 3, 4 AND 11-16 UNDER 35 U.S.C. §101

Claims 1, 3, 4 and 11-16 are rejected under 35 U.S.C. §101 as allegedly not being supported by either a specific utility or a well established utility. It is alleged that the combinatorial set of compounds prepared by the claimed methods are themselves the subject of research, and therefore lack utility. Applicant respectfully traverses this rejection.

Relevant Law

The Office has published guidelines for Examiners to use in determining when reviewing patent application for compliance with the "useful invention" (*i.e.*, "utility") requirement of 35 U.S.C. §§ 101 and 112, first paragraph:

- (a) Determine what the applicant has claimed, noting any specific embodiments of the invention.
- (b) Ensure that the claims define statutory subject matter (*i.e.*, a process, machine, manufacture, composition of matter, or improvement thereof).
- (c) If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (*e.g.*, properties or applications of a product or process), and (2) the utility is specific, substantial, and credible.

Examiners are also to review the claims and the supporting written description to determine if the applicant has asserted for the claimed invention any specific and substantial utility that is credible. If the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a "specific and substantial utility") and the assertion would be considered

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credible by a person of ordinary skill in the art, then a rejection based on lack of utility may not be imposed.

Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (*e.g.*, test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

The instant claims

Instant claim 4, as amended herein, is directed to a process for generating a combinatorial library by:

- (a) preparing a plurality of immobilized molecules selected from a nucleoside and a nucleotide; wherein each molecule contains 3 to 10 reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups on each immobilized molecule are independently removable under at least three different conditions; and
- (b) removing each blocking group and derivatizing the resulting reactive moiety in a preprogrammed, regioselective manner; wherein each member of the plurality of immobilized molecules is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial library.

Claim 11 further defines the reactive moieties. Claims 12-14 specify that the immobilized molecule is immobilized on a solid support, and specify the solid support. Claims 15 and 16 further define the linker used to immobilize the molecule on the solid support.

Utility of the claimed subject matter

The Office Action alleges that instant claims 1, 3, 4 and 11-26 are not supported by either a specific asserted utility or a well established utility. Applicant respectfully disagrees.

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Specific assertion of utility

It is alleged in the Office Action that the specification discloses that the compounds (oligonucleotides) are useful as drugs, which is not specific. In fact, the specification discloses that the compounds prepared by the claimed methods are useful in antisense and triplex DNA therapy (see, *e.g.*, the specification at page 2, lines 15-16 and page 14, lines 14-19).

The Office Action alleges that the specification does not identify the compounds which would be useful as drugs. It is respectfully submitted that such identification is not necessary. One of ordinary skill in the art would be able to determine, using standard assays known to those of skill in the art, which compounds of a library prepared by the instantly claimed methods would have the requisite biological activity. The biological activity required is a function of the disease, disorder or symptom to be treated. Thus, one of ordinary skill in the art would be able to readily determine, for a given disease, disorder or symptom, which compounds of a given library possess the required biological activity for that disease, disorder or symptom.

It is further alleged that there "is no basis in the specification upon which to conclude that *any* of the compounds encompassed by the library are, or will turn out to be, biologically active after testing," and that the "nucleic acid library prepared by the claimed method would require further research to identify useful oligonucleotides." It is respectfully submitted that the claimed method could be used to prepare libraries containing, in addition to new compounds, known antisense/triplex DNA agents. Therefore, these libraries would contain compounds which are biologically active. No further research would be required to determine that these libraries contained identifiable useful oligonucleotides. Furthermore, as noted above, one of skill in the art would be able to readily determine, using standard assays, which compounds possess requisite activity as antisense agents or for formation of triplex DNA, *e.g.*, for treatment of a given disease, disorder or symptom.

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Moreover, the Office Action has not set forth any reasons for doubting the asserted utility. It was well known in the art, at the time the application was filed, that oligonucleotide analogs are useful as antisense and triplex DNA agents. The instantly claimed methods provide methods for the preparation of such compounds. The instantly claimed methods are applicable to the preparation of a wide variety of oligonucleotide analogs, including known antisense and triplex DNA agents. Given this applicability of the methods, there is no reason for the Office to doubt the asserted specific utility.

Well established utility

It is further alleged in the Office Action that the combinatorial libraries produced by the instantly claimed methods are not supported by a well established utility. Applicant respectfully disagrees.

As noted in the Office Action, "a well established utility is a specific utility which is well known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art." As described in detail above, the combinatorial libraries prepared by the instantly claimed methods contain, *e.g.*, oligonucleotide analogs. It was well known at the time the application was filed that oligonucleotide analogs have utility as antisense or triplex DNA agents. See, *e.g.*, Uhlmann *et al.* (1990) *Chem. Rev.* 90:543-584 and Beaucage *et al.* (1993) *Tetrahedron* 49:6123-6194, cited in the application (copies enclosed).

Moreover, the libraries produced by the instantly claim process have utility in screening for compounds that are useful as antisense agents. Such libraries contain oligonucleotides and/or oligonucleotide analogs. These libraries were well known to those of skill in the art at the time the application was filed to have utility in screening for antisense agents.

It is further alleged in the application that "the compounds of the claimed libraries are not recognizable as analogous to compounds with a recognized

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pharmacological (or other) activity." Applicant notes that instant claims 4 and 11-16 are directed to processes for generating combinatorial libraries, not to combinatorial libraries themselves. Moreover, the compounds of the libraries produced by the instantly claimed methods are, *e.g.*, oligonucleotide analogs. As noted above, such compounds are well known to possess activity as antisense or triplex DNA therapeutic agents. Furthermore, the instantly claimed processes may be used to prepare known oligonucleotide analogs, among other compounds. Therefore, contrary to the assertion of the Office Action, data as to the activity of the compounds of the libraries produced by the instantly claimed methods is not required to establish the utility of instant claims 4 and 11-16 because some of the compounds that may be prepared by the methods are known to have antisense and triplex DNA activity.

Applicant respectfully requests reconsideration and removal of this rejection.

REJECTION OF CLAIMS 1, 3, 4 AND 11-16 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT

It is alleged in the Office Action that "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention." Applicant respectfully disagrees.

As described in detail above, the combinatorial libraries prepared by the instantly claimed methods are supported by both a specific utility and a well established utility. Therefore, one of skill in the art would know how to use the instantly claimed methods.

Applicant respectfully requests reconsideration and removal of this rejection.

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REJECTION OF CLAIMS 1, 3, 4 AND 11-16 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION

Claims 1, 3, 4 and 11-16 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is alleged that the instant claims do not recite the core structure M of the compounds or other identifying characteristics. While not agreeing with the propriety of this rejection, Applicant has cancelled claims 1 and 3 herein without prejudice or disclaimer. Claims 4 and 11-16 do not recite that the compounds have core structure M. Claim 4 recites that the immobilized compounds are selected from a nucleoside and a nucleotide. The Office Action notes that the specification is directed to oligonucleotide combinatorial libraries. Thus, it is respectfully submitted that the specification does provide adequate written description of the claims, as amended herein.

REJECTION OF CLAIMS 1, 3, 4 AND 11-16 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT

Claims 1, 3, 4 and 11-16 are rejected under 35 U.S.C. §112, first paragraph, as allegedly based on a specification which is not enabling. It is urged that, while being enabling for methods of oligonucleotide synthesis, the specification does not provide enablement for synthesis of any other kind of compounds such as oligosaccharides, lipids, vitamins, hormones, peptides or any other drug compounds. While not agreeing with this rejection, Applicant has cancelled claims 1 and 3 herein without prejudice or disclaimer. It is noted that claim 4 has been rewritten as an independent claim incorporating the limitations of the base claim. Claim 4 has also been amended herein to recited that the immobilized molecule is a nucleotide or nucleoside solely in the interest of advancing the prosecution of this application to allowance. Applicant reserves the right to file divisional applications directed to the cancelled subject

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matter. In view of these amendments and the above remarks, reconsideration and removal of this rejection is respectfully requested.

REJECTION OF CLAIM 16 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION

Claim 16 is rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is alleged that the specification does not provide an adequate representation regarding the allegedly open ended "derivatives thereof." While not agreeing with the propriety of this rejection, applicant has deleted this recitation from claim 16. This amendment to claim 16 is presented solely in the interest of advancing the prosecution of this application to allowance.

Applicant reserves the right to file divisional applications directed to any cancelled subject matter.

REJECTION OF CLAIMS 1, 3, 4 AND 11-16 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1, 3, 4 and 11-16 are rejected under 35 U.S.C. §112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant requests reconsideration of this rejection in view of the amendments to the claims herein and the following remarks. Applicant notes that claim 1 has been cancelled herein without prejudice or disclaimer. Claim 4 has been rewritten as an independent claim incorporating the limitations of claim 1. The amendments to the claims herein are made solely to advance the prosecution of this application to allowance and are not made to avoid any art of record. Applicant reserves the right to file divisional applications directed to any cancelled subject matter.

"A combinatorial set of molecules of core structure M"

Claim 1 is rejected as allegedly being indefinite for reciting "a combinatorial set of molecules of core structure M." In particular, clarification is requested as to the meaning of "combinatorial set of molecules." The recitation "combinatorial set of molecules" has been amended in claim 4 to recite "combinatorial library." A "combinatorial library," in the context of instant claim 4, is any set of molecules that may be prepared by the claimed process.

"Preparing a plurality of immobilized compounds of core structure M"

Claim 1 is rejected as allegedly being indefinite for reciting "preparing a plurality of immobilized compounds of core structure M." Clarification is requested as to how the compounds are prepared which are immobilized. Claim 4, as amended, recites a plurality of immobilized compounds molecules selected from a nucleoside and a nucleotide. The specification provides in the Examples methods for immobilizing such compounds. Reconsideration and removal of this rejection is respectfully requested.

"Said molecules contain a plurality of reactive moieties"

Claim 1 is rejected for reciting "said molecules contain a plurality of reactive moieties." Clarification is requested regarding what is meant by molecules contain a plurality of reactive moieties. Claim 4, as amended, recites "wherein each molecule contains 3 to 10 reactive moieties." It is respectfully submitted that this recitation makes clear that each molecule has 3 to 10 reactive moieties.

"At least three of the blocking groups..."

Claim 1 is rejected for reciting "at least three of the blocking groups are independently removable under at least three different conditions." Clarification is requested as to what is meant by at least three blocking groups. Claim 4, as amended, recites "at least three of the blocking groups on each immobilized molecule are independently removable under at least three different conditions."

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It is respectfully submitted that this recitation makes clear that the at least three blocking groups are on the same compound.

Clarification is also requested as to what is meant by at least three different conditions. As described in the specification (see, *e.g.*, page 5, lines 14-16), the "at least three different conditions" refer to conditions that selectively remove one of the blocking groups without removing the others (principle of orthogonality).

"Removing certain blocking groups"

Claim 1 is rejected for reciting "removing certain blocking groups." Clarification is requested as to what applicant means by certain blocking groups. As amended, claim 4 recites "removing each blocking group." These blocking groups are present on one molecule and are each selectively removed for derivatization of the molecule.

"Preprogrammed, regioselective manner"

Claim 1 is rejected for reciting "preprogrammed, regioselective manner." Clarification is requested as to the meaning of "preprogrammed" and "regioselective." "Preprogrammed" refers to the fact that each blocking group may be removed according to known conditions. Thus, one of skill in the art can predict, based on the library prepared, how to remove each blocking group selectively. Automatic or robotic machines may be employed for this purpose, but are not required. "Regioselective" is to be given its usual meaning in the art. Thus, each blocking group at a given position on the molecule may be removed selectively over other blocking groups in other positions of the molecule.

"The immobilized molecule"

Claim 3 is rejected for reciting "the immobilized molecule." It is alleged that there is insufficient antecedent basis for this recitation. While not necessarily agreeing with this rejection, applicant has cancelled claim 3 herein

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without prejudice or disclaimer. Applicant reserves the right to file divisional applications directed to any cancelled subject matter.

"Small molecule drug compound"

Claim 4 is rejected for reciting "small molecule drug compound."

Clarification is requested. While not necessarily agreeing with this rejection, claim 4 has been amended herein to delete this recitation without prejudice or disclaimer. Applicant reserves the right to file divisional applications directed to any cancelled subject matter.

Claims 11 and 12

Claims 11 and 12 are rejected for being dependent on non-elected claim 2. Claims 11 and 12 are amended herein to be dependent on claim 4. Claim 2 is cancelled herein without prejudice or disclaimer. Applicant reserves the right to file divisional applications directed to any cancelled subject matter.

"The molecule"

Claim 12 is rejected for reciting "the molecule." Claim 12 has been amended herein to recite "the immobilized molecules." It is respectfully submitted that this recitation has antecedent basis in base claim 4.

"The bottom of a microtiter"

Claim 13 is rejected for reciting "the bottom of a microtiter." Claim 13, as amended herein, recited "bottom surface of a microtiter plate." It is respectfully submitted that antecedent basis for this recitation is not required.

Markush format

Claim 13 is rejected as allegedly reciting an improper Markush group. Applicant has amended this claim as suggested by the Examiner in the interest of advancing the prosecution of this application to allowance.

Trademarks/trade names

Claim 14 is rejected for reciting trademarks and/or trade names. Applicant has amended claim 14 herein to replace these recitations with generic terminology. No new matter has been added.

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"Can b "

Claim 15 is rejected for reciting "can be" cleaved. Claim 15, as amended herein, recites "is cleavable." It is respectfully submitted that this recitation is not indefinite.

"Derivatives thereof"

Claim 16 is rejected for reciting "derivatives thereof." Applicant has amended claim 16 herein to delete this recitation solely in the interest of advancing the prosecution of this application to allowance. Applicant reserves the right to file divisional applications directed to any cancelled subject matter.

REJECTION OF CLAIMS 1, 3 AND 11 UNDER 35 U.S.C. §102(b) OVER MONTAL *et al.*

Claims 1, 3 and 11 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by the disclosure of Montal *et al.* (1990) *PNAS(USA)* 87(18):6929-6933. Applicant respectfully traverses this rejection.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundsciber Corp. v. U.S. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226,1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention.

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The instant claims

The instant claims are described above.

Differences between the disclosure of Montal *et al.* and the instant claims

Montal *et al.* discloses the 9-amino acid template K*KK*PGK*EK*G, where K* refers to N^ε-9-fluorenylmethoxycarbonyllysine, as a template for peptide synthesis. This template does not contain at least three blocking groups independently removable under at least three different conditions, as required by the instant claims. In fact, this template does not contain any blocking groups. As noted above, the instant claims are directed to processes for combinatorial library synthesis using compounds possessing at least three different blocking groups removable under at least three different conditions as a template. Montal *et al.* does not disclose such a process. Therefore, the instant claims are not anticipated by the disclosure of Montal *et al.*

REJECTION OF CLAIMS 1, 3, 4 AND 11-16 UNDER 35 U.S.C. §102(b) OVER SAUL *et al.*

Claims 1, 3, 4 and 11-16 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by the disclosure of Saul *et al.* (International Patent Application Publication No. WO 95/13538). Applicant respectfully traverses this rejection.

Relevant Law

The relevant law is described above.

The instant claims

The instant claims are described above.

Differences between the disclosure of Saul *et al.* and the instant claims

Saul *et al.* discloses a method of producing a chemical library containing a core molecule having 3-10 active functionalities. The cited reference discloses at page 22, line 28 to page 23, line 7 that "protective groups may have been employed" and that one example of an amino protective group is an Fmoc group. Saul *et al.* further discloses in this recitation that the protective groups may be removed under standard conditions. The reference does not disclose

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that each reactive moiety on the core molecule is blocked by a blocking group, wherein at least three of the blocking groups are independently removable under at least three different conditions, as required by the instant claims. Therefore, Saul *et al.* does not disclose each and every element of the instant claims. Thus, the instant claims are not anticipated by the disclosure of Saul *et al.*

REJECTION OF CLAIMS 1, 3 AND 4 UNDER 35 U.S.C. §102(b) OVER STENGELE *et al.*

Claims 1, 3 and 4 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by the disclosure of Stengele *et al.* (1990) *Tetrahedron Lett.* 31(18):2549-2552. Applicant respectfully traverses this rejection.

Relevant Law

The relevant law is described above.

The instant claims

The instant claims are described above.

Differences between the disclosure of Stengele *et al.* and the instant claims

Stengele *et al.* discloses synthesis of deoxyoligonucleotides using an NPE/NPEOC strategy. The cited reference discloses solid phase synthesis of deoxyoligonucleotides using dimethoxytrityl, NPE and NPEOC blocking groups. The cited reference discloses that the NPE and NPEOC groups are removed under the same conditions (see, page 1551, lines 4-5 of the cited reference). The reference does not disclose a strategy using at least three blocking groups that are independently removable under at least three different conditions, as required by the instant claims. Therefore, the instant claims are not anticipated by the disclosure of Stengele *et al.*

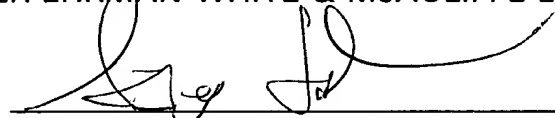
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In view of the above, reconsideration and allowance of the application is respectfully requested.

Respectfully submitted,
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